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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/708,786	11/08/2000	Sudhir Agrawal	47508.700	2469

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HALE AND DORR, LLP
60 STATE STREET
BOSTON, MA 02109

EXAMINER
GIBBS, TERRA C

ART UNIT	PAPER NUMBER
1635	12

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/708,786	Applicant(s) AGRAWAL, SUDHIR	
	Examiner Terra C. Gibbs	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's Amendment, filed 12/19/02, in Paper No. 11 is acknowledged.

Claims 1-27 are pending in the instant application.

Objections to the Specification

The Amendment to the Specification to correct the references to oligonucleotide 1 is acknowledged.

Nucleotide and/or Amino Acid Sequence Disclosure

The Amendment to the Specification to comply with the sequence rules is acknowledged.

Claim Objections

The Amendment to Claim 19 to correct the punctuation error is acknowledged.

Claim 9 is objected to because it contains a grammatical error. "I" should be replaced with "is". Appropriate correction is required.

Objections to the Specification

The specification is objected to because the legend of Figure 6 is unclear. For example, the lines representing "no treatment" and "CPT-11-25 mg" cannot be distinguished. Also, the lines representing "PBS" and "AS-1-10 mg" cannot be distinguished. Appropriate clarification is required.

Oath/Declaration

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). Applicant's Residence and Citizenship have been altered. No initials or dates have been made to verify changes. Appropriate correction is required.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows: An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Claim Rejections - 35 USC § 112

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

I. Applicant's traversal and request for reconsideration and withdrawal of the 35 U.S.C. 112, second paragraph rejection against claims 1, 10 and 19 has been fully considered, is found persuasive and is hereby withdrawn.

II. Applicant's traversal and request for reconsideration and withdrawal of the 35 U.S.C. 112, first paragraph rejection against claims 10-18 and 19-27 has been fully considered, is found persuasive and is hereby withdrawn.

Claims 19-27 are rejected under 35 USC, 112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The metes and bounds of the limitation "wherein the prodrug is present in an amount that would not be therapeutically effective in the absence of the a polyanion" in claim 19 is unclear. The limitation "wherein the prodrug is present in an amount that would not be therapeutically effective in the absence of the a polyanion" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claims 1, and 6-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is for Written Description.

Applicants Amendment to claim 1 recites a method for potentiating the activity of a prodrug comprising co-administering a polyanion (oligonucleotide) with the prodrug, provided that the polyanion (oligonucleotide) is not an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and wherein the oligonucleotide does not have the sequence of SEQ ID NO:1. Claims 6-9 depend from claim 1 and include all the limitations of claim 1, including the administration of anti-cancer prodrugs, specific prodrugs and prodrugs comprising specific agents, specific polyanions (oligonucleotides), and oligonucleotides comprising specific modified ribonucleosides.

The instant claims read on a method for statistically significantly potentiating the activity of a prodrug, the method comprising co-administering a polyanion (oligonucleotide) with the prodrug, provided that the polyanion (oligonucleotide) is not an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and wherein the oligonucleotide does not have the sequence of SEQ ID NO:1.

The claimed invention encompasses any polyanion (oligonucleotide) that statistically significantly potentiates the activity of any prodrug, any active compound or any anti-cancer compound, provided the polyanion (oligonucleotide) is not an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides does not have the sequence of SEQ ID NO:1, which includes sequences from any species, mutated sequences, polymorphic and allelic variants, splice variants, and so forth of any gene, provided the polyanion (oligonucleotide) is not an oligonucleotide of SEQ ID NO:1.

The specification as filed provides only a description of Campostar (CPT-11) as a prodrug and oligonucleotide phosphorothioate with 2'-O-methylribonucleosides at the 2 terminal 5' positions and 4 terminal 3' positions with the sequence of Oligo 1 (SEQ ID NO:1) and an oligonucleotide phosphorothioate with 2'-O-methylribonucleosides at the 2 terminal 5' positions and the 4 terminal 5' and 3' positions with the sequence of Oligo 2 (SEQ ID NO:1). However, the specification as filed, does not provide sufficient description that would allow one of skill in the art to use Campostar (CPT-11) as a prodrug and oligonucleotide phosphorothioates with 2'-O-methylribonucleosides at the 2 terminal 5' positions and 4 terminal 3' positions with the sequence of Oligo 1 (SEQ ID NO:1) and an oligonucleotide phosphorothioates with 2'-O-methylribonucleosides at the 2 terminal 5' positions and the 4 terminal 5' and 3' positions with

the sequence of Oligo 2 (SEQ ID NO:1) to predict the structures of any/all polyanion(s) (oligonucleotide(s)) that statistically significantly potentiate the activity of any/all prodrug(s), provided the polyanion (oligonucleotide) is not an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and does not have the sequence of SEQ ID NO:1.

The specification fails to describe the complete structure of a representative number of species of the claimed genus. See the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement (Vol. 66, No. 4, pages 1099-1111). These guidelines state that: "To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention." In the instant case, the specification does not describe or identify characteristics that can be used to distinguish species of the claimed genus.

Additionally, "[T]he skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is

part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence."

Applicant's specification does not provide a sufficient number of representative species of any polyanion (oligonucleotide) that statistically significantly potentiate the activity of any prodrug, provided the polyanion (oligonucleotide) is not an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and does not have the sequence of SEQ ID NO:1, which would allow one of skill in the art to predict the structures of all members of the claimed genus of compounds, including both prodrugs and oligonucleotides. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Therefore, the specification does not describe the claimed compounds in such full and concise terms so as to indicate that the applicant had possession of these compounds at the time of filing of this application. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.).

Claims 10 and 15-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is for Written Description.

Applicants Amendment to claim 10 recites a method for potentiating the activity of a prodrug comprising co-administering a polyanion (oligonucleotide) with the prodrug, wherein the polyanion (oligonucleotide) is administered before the prodrug. Claims 15-18 depend from claim 10 and include all the limitations of claim 10, including the administration of anti-cancer prodrugs, specific prodrugs and prodrugs comprising specific agents, specific polyanions (oligonucleotides), and oligonucleotides comprising specific modified ribonucleosides.

The instant claims read on a method for statistically significantly potentiating the activity of a prodrug, the method comprising co-administering a polyanion (oligonucleotide) with the prodrug, wherein the polyanion (oligonucleotide) is administered before the prodrug.

The claimed invention encompasses any polyanion (oligonucleotide) that statistically significantly potentiates the activity of any prodrug, any active compound or any anti-cancer compound, which includes sequences from any species, mutated sequences, polymorphic and allelic variants, splice variants, and so forth of any gene.

The specification as filed provides only a description of Campostar (CPT-11) as a prodrug and oligonucleotide phosphorothioate with 2'-O-methylribonucleosides at the 2 terminal 5' positions and 4 terminal 3' positions with the sequence of Oligo 1 (SEQ ID NO:1) and an oligonucleotide phosphorothioate with 2'-O-methylribonucleosides at the 2 terminal 5' positions and the 4 terminal 5' and 3' positions with the sequence of Oligo 2 (SEQ ID NO:1). However, the specification as filed, does not provide sufficient description that would allow one of skill in the art to use Campostar (CPT-11) as a prodrug and oligonucleotide phosphorothioates with 2'-O-methylribonucleosides at the 2 terminal 5' positions and 4 terminal 3' positions with the sequence of Oligo 1 (SEQ ID NO:1) and an oligonucleotide phosphorothioates with 2'-O-

methylribonucleosides at the 2 terminal 5' positions and the 4 terminal 5' and 3' positions with the sequence of Oligo 2 (SEQ ID NO:1) to predict the structures of any/all polyanion(s) (oligonucleotide(s)) that statistically significantly potentiate the activity of any/all prodrug(s).

The specification fails to describe the complete structure of a representative number of species of the claimed genus. See the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement (Vol. 66, No. 4, pages 1099-1111). These guidelines state that: "To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention." In the instant case, the specification does not describe or identify characteristics that can be used to distinguish species of the claimed genus.

Additionally, "[T]he skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is

required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence."

Applicant's specification does not provide a sufficient number of representative species of any polyanion (oligonucleotide) that statistically significantly potentiate the activity of any prodrug, which would allow one of skill in the art to predict the structures of all members of the claimed genus of compounds, including both prodrugs and oligonucleotides. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Therefore, the specification does not describe the claimed compounds in such full and concise terms so as to indicate that the applicant had possession of these compounds at the time of filing of this application. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.).

Claims 19 and 24-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is for Written Description.

Applicants Amendment to claim 19 recites a method for potentiating the activity of a prodrug comprising co-administering a polyanion (oligonucleotide) with the prodrug, wherein the prodrug is present in an amount that would not be therapeutically effective in the absence of

the polyanion (oligonucleotide). Claims 24-27 depend from claim 19 and include all the limitations of claim 19, including the administration of anti-cancer prodrugs, specific prodrugs and prodrugs comprising specific agents, specific polyanions (oligonucleotides), and oligonucleotides comprising specific modified ribonucleosides.

The instant claims read on a method for potentiating the activity of a prodrug comprising co-administering a polyanion (oligonucleotide) with the prodrug, wherein the prodrug is present in an amount that would not be therapeutically effective in the absence of the polyanion (oligonucleotide).

The claimed invention encompasses any polyanion (oligonucleotide) that statistically significantly potentiates the activity of any prodrug, any active compound or any anti-cancer compound, which includes sequences from any species, mutated sequences, polymorphic and allelic variants, splice variants, and so forth of any gene.

The specification as filed provides only a description of Camptosar (CPT-11) as a prodrug and oligonucleotide phosphorothioate with 2'-O-methylribonucleosides at the 2 terminal 5' positions and 4 terminal 3' positions with the sequence of Oligo 1 (SEQ ID NO:1) and an oligonucleotide phosphorothioate with 2'-O-methylribonucleosides at the 2 terminal 5' positions and the 4 terminal 5' and 3' positions with the sequence of Oligo 2 (SEQ ID NO:1). However, the specification as filed, does not provide sufficient description that would allow one of skill in the art to use Camptosar (CPT-11) as a prodrug and oligonucleotide phosphorothioates with 2'-O-methylribonucleosides at the 2 terminal 5' positions and 4 terminal 3' positions with the sequence of Oligo 1 (SEQ ID NO:1) and an oligonucleotide phosphorothioates with 2'-O-methylribonucleosides at the 2 terminal 5' positions and the 4 terminal 5' and 3' positions with

the sequence of Oligo 2 (SEQ ID NO:1) to predict the structures of any/all polyanion(s) (oligonucleotide(s)) that statistically significantly potentiate the activity of any/all prodrug(s).

The specification fails to describe the complete structure of a representative number of species of the claimed genus. See the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement (Vol. 66, No. 4, pages 1099-1111). These guidelines state that: "To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention." In the instant case, the specification does not describe or identify characteristics that can be used to distinguish species of the claimed genus.

Additionally, "[T]he skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai

Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence."

Applicant's specification does not provide a sufficient number of representative species of any polyanion (oligonucleotide) that statistically significantly potentiate the activity of any prodrug, which would allow one of skill in the art to predict the structures of all members of the claimed genus of compounds, including both prodrugs and oligonucleotides. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Therefore, the specification does not describe the claimed compounds in such full and concise terms so as to indicate that the applicant had possession of these compounds at the time of filing of this application. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.).

Claims 1-9 are rejected under 35 USC, 112 first paragraph, because the specification while being enabled for a method for potentiating the activity of the prodrug Camptosar (CPT-11), comprising co-administering an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and the sequence of SEQ ID NO:1, does not reasonably provide enablement for a method for potentiating the activity of a prodrug comprising co-administering a polyanion (oligonucleotide) with the prodrug, provided that the polyanion (oligonucleotide) is not an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and wherein the oligonucleotide does not have the sequence of SEQ ID NO:1. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 1 is drawn to a method for potentiating the activity of a prodrug comprising co-administering a polyanion (oligonucleotide) with the prodrug, provided that the polyanion (oligonucleotide) is not an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and wherein the oligonucleotide does not have the sequence of SEQ ID NO:1. Claims 2-9 depend from claim 1 and include all the limitations of claim 1, including the administration of anti-cancer prodrugs, specific prodrugs and prodrugs comprising specific agents, specific polyanions (oligonucleotides), and oligonucleotides comprising specific modified ribonucleosides.

The instant invention specification provides the survival times of mice co-administered with the prodrug Camptosar (CPT-11) and Oligo 1 or Oligo 2 (see Figures 1-6 and Examples 1-3) which are specific modified ribonucleosides of SEQ ID NO:1.

The instant specification does not describe how to make and/or use that polyanion (oligonucleotide) which is not an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and wherein the oligonucleotide does not have the sequence of SEQ ID NO:1 (see the 112, first paragraph rejection against claims 1, and 6-9 for Written Description on page 4). For example, will any prodrug administered with any polyanion potentiate the effect of the prodrug? More specifically, will the prodrug, CPT-11, administered with any polyanion potentiate the effect of the prodrug?

In view of the breadth of the claims, the amount of direction provided by the instant specification, and the quantity of experimentation needed to make/or use the invention based on

the content of the disclosure, the specification as filed does not provide adequate guidance or examples that would show by correlation how one skilled in the art would practice the claimed invention over the scope claimed without having to engage in trial and error or undue experimentation. The specification as filed describes a method for potentiating the activity of the prodrug, Camptosar (CPT-11), comprising co-administering an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and the sequence of SEQ ID NO:1. However, the instant specification does not describe a method for potentiating the activity of a prodrug comprising co-administering a polyanion (oligonucleotide) with the prodrug, provided that the polyanion (oligonucleotide) is not an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and wherein the oligonucleotide does not have the sequence of SEQ ID NO:1.

Due to the lack of specific guidance in the specification as filed and the lack of correlation between a method for potentiating the activity of the prodrug Camptosar (CPT-11), comprising co-administering an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and the sequence of SEQ ID NO:1 and a method for potentiating the activity of a prodrug comprising co-administering a polyanion (oligonucleotide) with the prodrug, provided that the polyanion (oligonucleotide) is not an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and wherein the oligonucleotide does not have the sequence of SEQ ID NO:1, one of skill in the art would require specific guidance to practice the current invention. The current specification does not provide such guidance to a method for potentiating the activity of a prodrug comprising co-administering a polyanion (oligonucleotide) with the prodrug, provided that the polyanion (oligonucleotide) is not an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and wherein the oligonucleotide does not have the

sequence of SEQ ID NO:1 and one of skill in the art would be required to perform trial and error or undue experimentation to practice the invention over the scope claimed. It is noted that the breadth of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Accordingly, limiting the scope of the claimed invention to a method for potentiating the activity of the prodrug Camptosar (CPT-11), comprising co-administering an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and the sequence of SEQ ID NO:1, is proper.

Claims 10-18 are rejected under 35 USC, 112 first paragraph, because the specification while being enabled for a method for potentiating the activity of the prodrug Camptosar (CPT-11), comprising the administration of an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and the sequence of SEQ ID NO:1, wherein the oligonucleotide is administered before CPT-11, does not reasonably provide enablement for a method for potentiating the activity of a prodrug comprising co-administering a polyanion (oligonucleotide) with the prodrug, wherein the polyanion (oligonucleotide) is administered before the prodrug. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 10 is drawn to a method for potentiating the activity of a prodrug comprising co-administering a polyanion (oligonucleotide) with the prodrug, wherein the polyanion (oligonucleotide) is administered before the prodrug. Claims 11-18 depend from claim 10 and

include all the limitations of claim 10, including the administration of anti-cancer prodrugs, specific prodrugs and prodrugs comprising specific agents, specific polyanions (oligonucleotides), and oligonucleotides comprising specific modified ribonucleosides.

The instant invention specification provides the survival times of mice co-administered with the prodrug Camptosar (CPT-11) and Oligo 1 or Oligo 2 (see Figures 1-6 and Examples 1-3) which are specific modified ribonucleosides of SEQ ID NO:1.

The instant specification does not describe how to make and/or use any prodrug other than CPT-11 or any polyanion (oligonucleotide) other an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and the sequence of SEQ ID NO:1 (see the 112, first paragraph rejection against claims 10 and 15-18 for Written Description on page 7). For example, will any prodrug administered with any polyanion potentiate the effect of the prodrug? More specifically, will the prodrug, CPT-11, administered with any polyanion potentiate the effect of the prodrug?

In view of the breadth of the claims, the amount of direction provided by the instant specification, and the quantity of experimentation needed to make/or use the invention based on the content of the disclosure, the specification as filed does not provide adequate guidance or examples that would show by correlation how one skilled in the art would practice the claimed invention over the scope claimed without having to engage in trial and error or undue experimentation. The specification as filed describes a method for potentiating the activity of the prodrug Camptosar (CPT-11), comprising co-administering an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and the sequence of SEQ ID NO:1. However, the instant specification does not describe a method for potentiating the activity of any prodrug, other than CPT-11, comprising the administration of any polyanion (oligonucleotide) with the prodrug,

other an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and the sequence of SEQ ID NO:1 and wherein the polyanion (oligonucleotide) is administered before the prodrug.

Due to the lack of specific guidance in the specification as filed and the lack of correlation between a method for potentiating the activity of the prodrug Camptosar (CPT-11), comprising the co-administration of an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and the sequence of SEQ ID NO:1, and a method for potentiating the activity of a prodrug comprising the administration a polyanion (oligonucleotide) with the prodrug, wherein the polyanion (oligonucleotide) is administered before the prodrug, one of skill in the art would require specific guidance to practice the current invention. The current specification does not provide such guidance to a method for potentiating the activity of any prodrug, other than CPT-11, comprising the administration of any polyanion (oligonucleotide) with the prodrug, other an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and the sequence of SEQ ID NO:1, and one of skill in the art would be required to perform trial and error or undue experimentation to practice the invention over the scope claimed. It is noted that the breadth of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Accordingly, limiting the scope of the claimed invention to a method for potentiating the activity of the prodrug Camptosar (CPT-11), comprising the administration of an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and the sequence of SEQ ID NO:1, wherein the oligonucleotide is administered before CPT-11, is proper.

Claim 19-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 19 is drawn to a method for potentiating the activity of a prodrug comprising co-administering a polyanion (oligonucleotide) with the prodrug, wherein the prodrug is present in an amount that would not be therapeutically effective in the absence of the polyanion (oligonucleotide). Claims 20-27 depend from claim 19 and include all the limitations of claim 19, including the administration of anti-cancer prodrugs, specific prodrugs and prodrugs comprising specific agents, specific polyanions (oligonucleotides), and oligonucleotides comprising specific modified ribonucleosides.

The instant invention specification provides the survival times of mice co-administered with the prodrug Camptosar (CPT-11) and Oligo 1 or Oligo 2 (see Figures 1-6 and Examples 1-3) which are specific modified ribonucleosides of SEQ ID NO:1.

The instant specification does not describe how to make and/or use any prodrug other than CPT-11 or any polyanion (oligonucleotide) other an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and the sequence of SEQ ID NO:1 (see the 112, first paragraph rejection against claims 19 and 24-27 for Written Description on page 10). For example, will any prodrug administered with any polyanion potentiate the effect of the prodrug? More specifically, will the prodrug, CPT-11, administered with any polyanion potentiate the effect of the prodrug? Furthermore, the specification does not describe the limitation "wherein the prodrug is present in an amount that would not be therapeutically effective in the absence of the

polyanion (oligonucleotide)" as defined in Claim 19 (see the 112, second paragraph rejection against claims 19-27 for metes and bounds of the invention).

In view of the breadth of the claims, the amount of direction provided by the instant specification, and the quantity of experimentation needed to make/or use the invention based on the content of the disclosure, the specification as filed does not provide adequate guidance or examples that would show by correlation how one skilled in the art would practice the claimed invention without having to engage in trial and error or undue experimentation. The specification as filed describes a method for potentiating the activity of the prodrug Camptosar (CPT-11), comprising co-administering an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and the sequence of SEQ ID NO:1. However, the instant specification does not describe a method for potentiating the activity of any prodrug, other than CPT-11, comprising the administration of any polyanion (oligonucleotide) with the prodrug, other an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and the sequence of SEQ ID NO:1 and wherein the prodrug is present in an amount that would not be therapeutically effective in the absence of the polyanion (oligonucleotide).

Due to the lack of specific guidance in the specification as filed and the lack of correlation between a method for potentiating the activity of the prodrug Camptosar (CPT-11), comprising the co-administration of an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and the sequence of SEQ ID NO:1, and a method for potentiating the activity of a prodrug comprising the administration a polyanion (oligonucleotide) with the prodrug, wherein the prodrug is present in an amount that would not be therapeutically effective in the absence of the polyanion (oligonucleotide), one of skill in the art would require specific

guidance to practice the current invention. The current specification does not provide such guidance to a method for potentiating the activity of any prodrug, other than CPT-11, comprising the administration of any polyanion (oligonucleotide) with the prodrug, other an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and the sequence of SEQ ID NO:1, and one of skill in the art would be required to perform trial and error or undue experimentation to practice the invention.

Claim Rejections - 35 USC § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

I. Applicant's traversal and request for reconsideration and withdrawal of the 35 U.S.C. 102(b) rejection against claims 1, 10 and 19 has been fully considered, is found persuasive, and is hereby withdrawn.

Claims 10, 14, 15, 16, 17 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al [US Patent No. 6,013,786].

Claim 10 is drawn to a method for statistically significantly potentiating the activity of a prodrug comprising co-administering a polyanion (oligonucleotide) with the prodrug, wherein the polyanion (oligonucleotide) is administered before the prodrug. Claims 14-17 depend from claim 10 and include all the limitations of claim 10, including specific prodrugs and prodrugs comprising specific agents, specific polyanions (oligonucleotides), and oligonucleotides comprising specific modified ribonucleosides.

Chen et al teach JAR cells treated with prodrug campothecin (CPT) and a phosphorothioate oligonucleotide targeting mdm2 (see Figures 7A-7C). Chen et al further teach that CPT alone activated he p53 reporter only by 3-4 fold, however, with the phosphorothioate oligonucleotide targeting mdm2 resulted in a 17-fold activation of the p53 reporter. Chen et al also teach co-administration of CPT and the phosphorothioate oligonucleotide targeting mdm2 resulted in up to 90-fold induction of p53 activity. Chen et al further teach a synergistic effect between the phosphorothioate oligonucleotide targeting mdm2 and CPT was observed in MCF-cells (see column 16, lines 16-37).

Therefore, Chen et al anticipate the current invention.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

I. Applicant's traversal and request for reconsideration and withdrawal of the 35 USC 103(a) rejection against claims 1-27 has been fully considered, but is not found persuasive and is maintained for the reasons of record as set forth in the Office Action dated 6/19/02.

Applicants argue that Tortora et al. teach the synergistic effect of chemotherapeutic agents that are administered prior to the administration of a sequence-specific oligonucleotide targeted to protein kinase A. Applicants further argue that the chemotherapeutic agents tested by Tortora et al. are not prodrugs.

Applicants argue that Wang et al. teach a method for potentiating the activity of a

chemotherapeutic agent, HCPT, by administering an antisense oligonucleotide targeted to mdm-2. Applicants further argue that HCPT is not a prodrug.

Applicants argue that Chen et al. teach a method for potentiating the activity of a chemotherapeutic agent, HCPT, by administering an antisense oligonucleotide targeted to mdm-2. Applicants further argue that HCPT is not a prodrug.

Applicants argue that Baracchini et al. teach antisense oligonucleotides targeted to mdm, and the use of these oligonucleotides to reverse resistance to chemotherapeutic agents. Applicants further argue that Baracchini et al. do not teach a method for potentiating the activity of a prodrug by co-administering a polyanion (oligonucleotide) and a prodrug.

Applicant's arguments have not been found persuasive because Chen et al teach potentiation of the activity of the prodrug CPT-11 by co-administering a phosphorothioate oligonucleotide targeting mdm2 resulted in a 17-fold activation of the p53 reporter (see Figures 7A-7C).

As argued in the previous Office Action, it would have been obvious to one of ordinary skill in the art to co-administer a prodrug with a phosphorothioate oligonucleotide in a manner that potentiates the activity of the prodrug because this would lessen the deleterious side effects. As argued in the previous Office Action, one of ordinary skill in the art would have been motivated to potentiate the activity of a cytotoxic prodrug, such as CPT-11, with phosphorothioate oligonucleotides since Tortora et al. taught synergistic inhibition of human cancer cell growth by cytotoxic drugs and phosphorothioate antisense oligonucleotides. As argued in the previous Office Action, one of ordinary skill in the art would have had a reasonable expectation of success potentiating the activity of a cytotoxic prodrug, such as CPT-11, with

phosphorothioate oligonucleotides because Chen et al. have taught potentiation of the activity of the prodrug CPT-11 by co-administering a phosphorothioate oligonucleotide targeting mdm2 resulted in a 17-fold activation of the p53 reporter. As argued in the previous Office Action, one of ordinary skill in the art would have been motivated to modify the phosphorothioate oligonucleotide to include oligonucleotide phosphorothioate oligonucleotides with 2'-O-methylribonucleoside modifications at varying positions and had a reasonable expectation of success since the art taught the use of modified phosphorothioate oligonucleotides as particularly useful therapeutics for oral administration (Baracchini et al.).

As argued in the previous Office Action, the invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-8693 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
March 10, 2003

RAM R. SHUKLA, P...
PATENT EXAMINER